REMARKS

Applicants thank the Examiner for withdrawing the finality of the previous Office Action.

Claims 1, 6, and 11 have been amended by incorporating the subject matter of claim 3, 8, and 13, respectively.

Care has been taken not to introduce any new matter.

The Present Invention

The present invention is directed to a new and unobvious combination of specified retinoids and specified retinoid boosters **in a dual compartment package, where the compartments are joined together and made of aluminum,** intended to avoid chemical degradation of retinoids that would be caused by contact with the retinoid boosters. The specified retinoid boosters, despite boosting the effect of specified retinoids on the skin, tend to *destabilize* the specified retinoids in the composition. The claimed retinoid boosters are among a specific list that has been demonstrated *with objective evidence on page 37 of the Specification* and in the accompanying Rule 132 Declaration to de-stabilize retinoids to a greater extent than the retinoids would be unstable in the absence of the boosters, i.e., there is a greater stability problem. The retinoid/retinoid booster combinations, *both of which are intended for the same skin benefit and to be applied substantially at the same time,* are maintained in separate compartments of a package and the retinoid composition is kept out of contact with oxygen to promote its stability against chemical degradation and to avoid further instability that would be caused by contact with retinoid boosters.

The independent claims herein are further limited by dependent claims, some of which, i.e., 2, 7 and 12, are directed to retinoid combinations with *at least 2 boosters.* **The Rule 132 Declaration accompanying this Amendment is supportive of the claimed benefit.**

An unexpected result of the present invention is that compositions that do not contain retinoic acid behave analogously to treatment with retinoic acid (i.e. mimick), as if they did contain the most active form of retinoid, i.e., retinoic acid, while maintaining retinoid stability over time.

Claim Rejections - 35 USC § 103

Claims 1-15 and 17-18 Are Not Obvious

Claims 1-2, 4-7, 9-12, 14-15 and 17-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Burger et al. (USPN 5,759,556) *and Granger 5,716,627* in view of Liu et al. (USPN 5,976,555) and further in view of Suares et al. (USPN 5,914,116). **Claims 3, 8 and 13** were rejected under 35 U.S.C. 103(a) as being unpatentable over Burger et al. *'556* in view of Suares et al. (USPN 5,914,116) and Liu et al. (USPN 5,976,555) and Remington's Pharmaceutical Sciences (Remington). According to the one or more of the Office Actions, Remington in a subsection entitled "pharmaceutical containers" in the chapter on stability of pharmaceutical products teaches that aluminum containers are widely used in the pharmaceutical products.

Independent Claims 1, 6, and 11 have been amended by incorporating the subject matter of claims 3, 8, and 13, respectfully.

Applicants respectfully traverse. *Burger* ***'556*** does not render the present invention obvious alone or in combination with the secondary references, as discussed above, nor in combination with Granger '627. The secondary references do not remedy the deficiencies of Burger et al.

According to the Office Action, Burger **'556** disclose a skin conditioning composition comprising a compound selected from retinol or retinyl ester in

combination with *alpha-ionones and damascones*. The Office Action admits that Burger et al does not disclose the first compartment for storing retinol or retinyl ester kept out of contact with oxygen, and the second compartment for storing *alpha-ionone*, and the first and second compartments being joined together; and avoiding chemical degradation of retinol or retinyl ester in the first composition that would be caused by contact with *alpha-ionone* in the second composition.

Liu et al. and Suares et al. do not remedy the deficiencies of *Burger et al.* In fact, none of the references cited in the Office Action teach or suggest the need or the solution for stabilizing retinoid compositions in the presence of retinoid enhancing actives. Therefore, although dual purpose single formulation cosmetic products have been developed in the cited art, only in hindsight, with the benefit of the disclosure of the present invention, is the need for stable cosmetic compositions that attenuate the existing problems of retinoid stability in the presence of boosters met.

Liu et al. merely restate the problem. Liu et al. merely state an invitation to invent by restating that retinoids are unstable. Liu et al. do not address the problem to which the present invention is addressed, i.e., alleviating the additional instability contributed by boosters. (At most, Liu et al. provide a different solution – i.e. formulating in an emulsion with a specifically defined stabilizer system, but all in one composition.) The combination cited references does not arrive at the subject matter of the present invention as claimed. Although Liu et al. describe a container for storing the composition so that it is out of contact with oxygen, the container is described in combination with a retinoid composition with an emulsifier system and a co-emulsifier alone and does not protect the retinoid from degradation due to contact with retinoid boosters.

Further according to the Office Action, Suares et al. (USPN 5,914,116) teaches a a first and second composition stored in separate containers joined together. *However, the product of Suares et al. includes a first composition for obtaining a first skin benefit (e.g., Vitamin A palmitate) and a second composition for obtaining a second and different benefit, and the two compositions are part of a regimen teaching their application at different times of day.* The Office Action admits that Suares et al. (USPN 5,914,116) does not teach that the first and/or second compartments keep the respective compositions out of contact with oxygen, neither does it teach that the two compartments are made of aluminum, *nor does it teach the two compositions aimed at the same skin benefit and intended to be applied at substantially the same time.*

Evidence of Unexpected Results Has Been Presented

Applicants have presented evidence of unexpected results in the Specification and accompanying Declaration. Independent claims 1, 6 and 11 relate to specific booster compounds that are shown to de-stabilize the claimed retinoids to a greater extent than the degree of instability in the absence of the boosters. See the table on page 37 of the Specification. For example, the results in the Table show that *alpha-ionone (B1 booster)* increases the rate of retinol loss by a factor of 1.3. Similarly, it can be seen that all the claimed boosters significantly increase the rate of retinol loss. Therefore, the **presence of the boosters necessitates separate compartments for the two compositions**, more so than the cited art.

Applicants have shown the advantages of employing more than a single booster with respect to increase in CRABPII production.

These are unexpected results, not addressed by any of the cited references alone or in combinaion.

As discussed above, *Burger et al* is an insufficient primary reference and the secondary references do not remedy its deficiencies. Furthermore, there is no motivation to combine *Burger et al* with Remington, Suares et al. and Liu et al. because Remington deals with high temperature storage. High temperature storage is not relevant to the present invention.

Claim 16 Is Not Obvious Over Burger in View of Granger and Liu and Suares

Claim 16, which specifies a booster combination of **climbazole** (B5) with **alpha-ionone** (B1) and/or **damascenone**, was rejected under 35 U.S.C. 103(a) as being unpatentable over Burger et al '556 in view of Granger et al. (USPN 5,716,627) in view of Suares et al. (USPN 5,914,116) and Liu et al. (USPN 5,976,555).

Burger **'556** do not disclose climbazole and Granger **'627** is cited for disclosing a skin conditioning composition comprising a) retinol or retinyl ester, b) azole, *e.g., climbazole*, c) a fatty acid amide such as linoleoyl-DEA. However, admittedly, Granger et al '627 does not disclose the first compartment for storing retinol or retinyl ester kept out of contact with oxygen, and the second compartment for storing *climbazole*, and the first and second compartments being joined together; and avoiding chemical degradation of retinol or retinyl ester in the first composition that would be caused by contact with *climbazole or alpha ionone* in the second composition.

As stated previously, the independent claim 11 and claim 16 dependent thereon relate to specific booster compounds that are shown to de-stabilize the claimed retinoids to a greater extent than the degree of instability in the absence of the boosters. See the table on page 37 of the Specification. For example, the results in the Table show that *alpha-ionone* increases the rate of retinol loss by a factor of 1.3. According to the accompanying Declaration, retinol is only 2/3 as stable in the presence of citral. Similarly, it can be seen that all the claimed boosters significantly increase the rate of retinol loss. Therefore, the **presence of the boosters necessitates separate compartments for the two compositions**, more so than the cited art. *These are unexpected results.*

Invention Must Be Viewed As a Whole

It is improper to pick and choose pieces of a variety of art to come up with a rejection as in the Office Action. There must be some suggestion or motivation for combinations of the references, which must be viewed as a whole.

Burger fails to disclose climbazole. Burger and Granger fail to disclose the first compartment for storing retinol or retinyl ester kept out of contact with oxygen; and first and second compartments being joined together; and avoiding chemical degradation of retinol or retinyl ester in the first composition. Nor do Burger, Liu and Suares disclose the first compartment made of aluminum. Remington's is non-analogous because it refers to high temperature storage of pharmaceuticals.

If fact, none of the references cited in the Office Action teach or suggest the need or the solution for stabilizing retinoid compositions in the presence of retinoid

enhancing actives. Therefore, although dual purpose single formulation cosmetic products have been developed in the cited art, only in hindsight, with the benefit of the disclosure of the present invention, is the need for stable cosmetic compositions that attenuate the existing problems of retinoid stability in the presence of boosters met. Even if combined, Applicants respectfully submit that, since the independent claims are in condition for allowance, those claims that depend from them are also in condition for allowance.

An obviousness rejection is proper only when "the subject matter as a whole would have been obvious at the time the invention was made ..." (emphasis added). 35 U.S.C. 103. Applicants respectfully submit that the Office Action has improperly chosen certain aspects of one reference and combined them with aspects of other references, without showing where the motivation is to combine them to come up with the subject matter of the present invention as a whole, within the meaning of 35 U.S.C. 103. Applicants submit that the pending claims are not obvious over the cited references, under 35 U.S.C. 103, especially in view of the present Amendment. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim Rejections –Double Patenting

Applicants traverse these rejections. Applicants respectfully maintain that the double patenting rejections under the judicially created doctrine of obviousness-type double patenting is improper for the reasons discussed above. Nevertheless, in the interest of progressing the present application to issue without delay, to the extent any double patenting rejections may remain, Applicants would be willing to supply a terminal disclaimer upon indication of allowability of the present claims.

In view of the foregoing amendments and comments, Applicants request the Examiner to reconsider the rejection and now allow the claims.

Respectfully submitted,

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J6666(C)
UNUS #: Y2-R554-EDG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Granger et al.
Serial No.: 10/007,869
Filed: November 8, 2001
For: STABLE SKIN CARE PRODUCT CONTAINING A RETINOID AND A RETINOID BOOSTER SYSTEM IN A DUAL COMPARTMENT PACKAGE

Group: 1617
Examiner: Jiang, S. A.
Edgewater, New Jersey 07020
JULY 28, 2004

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

I, Susanne Teklits Iobst, residing at 89 Stelling Avenue, Maywood, NJ 07607 do hereby declare that:

1. I am a citizen of the United States.

2. My educational and technical background in the field of Biochemistry is as follows:

(a) I received a Bachelor of Science Degree in Biochemistry from Lehigh University in 1986.

(b) I received a Master of Science Degree in Chemistry from Stevens Institute of Technology in 1989.

(c) I received a Doctorate of Philosophy from the Department of Biochemistry and Molecular Biophysics at Columbia University in 1995.

(d) I joined my present employer Unilever in 1986 and I currently have the title Research Scientist, located in Edgewater, NJ.

3. I have read Granger et al., US Patent Application no. 10/007,869 filed November 8, 2001.

4. The following experiments were conducted in support of the above-cited Granger et al. patent application.

5. **Retinol Stability and Clinical Assessment of CRABPII**

Clinical Methodology

Compounds were formulated in a PG/EtOH vehicle with retinol. Individual subjects were treated for two times/day for 4 days with the test compound. On the 5th day, a skin sample was taken. Protein was isolated from the skin sample and a Western blot was performed using a CRABPII antibody. The % increase in CRABPII was measured in relation to the amount of CRABPII protein that was generated from a sample containing retinol alone.

Efficacy Data: Example A

Compound	Increase in CRABPII production
Climbazole	17%
Climbazole/Damascenone/AMEA/Cetyl Alcohol	22%

Efficacy Data: Example B

Compound	Increase in CRABPII production
2.5% cetyl alcohol	50%
0.5% quercetin	8%
2.5% cetyl alcohol, 0.2%damascenone, 0.5% quercetin	121%

Retinol Stability Data: Example 1

Compound	Retinol stability @21 days at 30 C
Retinol	62%
Retinol/Citral	40%
Retinol/citral/glycyrretinic acid/quercetin	37.6%

6. I conclude the following from these experiments:

Based on the analysis above, it is clear that Retinol stability is significantly diminished in the presence of boosters, creating a greater necessity for its stabilization than in the absence of boosters. Example 1 shows the significant decrease in retinol stability in the presence of the citral booster.

A combination of boosters gives a greater increase in CRABPII production than a single booster. With some of the combinations in the

Tables, the size of the effect is greater than additive, indicating a strongly synergistic result.

Example A shows that combining retinol with at least two boosters, e.g., climbazole with damascenone, leads to greater increase in CRABPII production.

7. I declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and may jeopardize the validity of the application or any patent issuing thereon.

Dated: JULY 28 , 2004

By: 

Susanne Teklits Iobst

Title: Research Scientist